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REVIEW

Patch testing: what allergists should know

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Summary
Patch testing is a standardized, *in vivo* diagnostic test for type IV hypersensitivity reactions, resulting in allergic contact dermatitis, which clinically resembles eczema. Common allergens include fragrance chemicals, hair dyes, metals, rubber accelerators and preservatives. Known allergens at particular concentrations in optimal vehicles are tested on the upper back under occlusion for 2 days. Readings according to international criteria are usually performed on days 2 and 4. Irritant reactions can closely resemble allergic ones, and further tests may be necessary to discriminate. Interpretation of the relevance of the reactions can also be difficult, perhaps requiring repeated open application testing, work-site visits etc. Monitoring of trends in patch test positivity can be effective in primary prevention of type IV allergy.

Introduction

Patch testing is a complex but effective means of investigating type IV allergic reactions which cause allergic contact dermatitis (ACD). It is usually performed by dermatologists according to international guidelines. The evaluation of the reactions is critical, as the morphology of irritant and allergic responses may be very similar. Establishing relevance of any reaction is also important, to allow the patient to avoid relevant allergens. Quality of life indices are improved when contact allergy is correctly investigated [1]. This overview of patch testing is not meant to be exhaustive but hopefully gives a flavour of the complexity of the testing process. Visiting a unit performing patch tests well gives an invaluable insight into this form of *in vivo* diagnostic testing.

History of patch testing

Although specific contact reactions had been reported even in antiquity, it was not until the end of the 19th century that a rigorous approach to testing was adopted. Josef Jadassohn developed a standardized epicutaneous test to investigate a reaction to mercury-containing compounds. This patch test used an occlusive dressing and the test material was occluded for 24 h. At around the same time, Jean-Henri Fabre used blotting paper to occlude caterpillar extracts and this was held against the skin with bandages for 24 h, resulting in red, swollen skin with oozing serous fluid (quoted in Foussereau [2]). Over the next 60–70 years, small incremental improvements on technique were made, but there was a lack of standardization. Bruno Bloch (a pupil of Jadassohn) was the first to describe a grading system for the intensity of the reactions on epicutaneous testing. He also described the concepts of cross-sensitization, (what is now known as) systemic allergic dermatitis and even proposed a screening series of allergens for routine testing (quoted in Lachapelle [3]). This screening series was further developed by another important figure, Poul Bonnevie [4]. A significant step towards standardizing patch test technique was made with the founding of the International Contact Dermatitis Research Group in 1967 [3]. This focussed on a number of important issues such as which vehicles to use, allergen concentration, grading of results etc.

Basic mechanisms in contact allergy

Contact allergens are typically low molecular weight chemicals that are able to gain access to the viable epidermis. They have diverse chemical structures (e.g. from nickel ions to proteins) and are haptens, forming stable associations with proteins to trigger cutaneous immune responses (sensitization). Allergen-activated Langerhans cells migrate to the regional lymph nodes where they are recognized by specific T cells. These T cells then proliferate under the influence of IL-1 released by the Langerhans cells, triggering an autocrine cascade.

Effector T cells are then released into the circulation. If the allergen is re-encountered, the effector phase is activated, with release of abundant pro-inflammatory cytokines and chemokines, which induce an eczematous reaction which usually is maximal at around 48 h after exposure [5, 6]. Recently, Toll-like receptor 4 has been shown to be activated by exposure to nickel leading to an inflammatory response [7]. Whether or not this will be replicated with other allergens remains to be seen.

Studies on genetic and immunological factors in contact allergy are hampered by the fact that mechanisms may vary for sensitization and elicitation and different allergens may induce different pathways. Nevertheless, small studies have shown genetic susceptibility factors with a variety of different allergens (notably, rapid acetylators with a NAT2*4 wild-type allele have been shown to be more common in contact allergic groups than in controls) [8]. The TNFA-308 G/A polymorphisms may influence sensitization. An increased frequency of GA or AA genotypes in para-phenylenediamine-allergic individuals compared with non-allergic controls has been demonstrated [9]. There has been recent interest in filaggrin mutations in contact allergy, but this remains unproven.

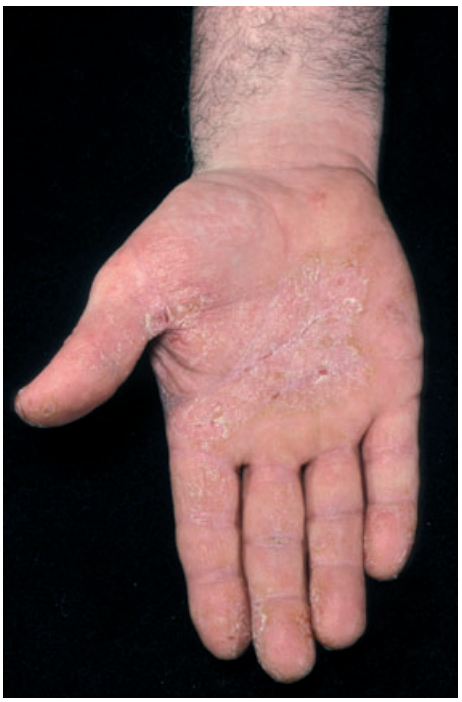

Fig. 1. Dermatitis with both irritant and allergic components. This patient was positive to potassium dichromate, which was occupationally relevant as he worked with tanned leather.

Clinical aspects

Eczematous reactions on the skin may be of endogenous, irritant or allergic origin (or a combination of these). Hence, a precise diagnosis may sometimes only be possible with information from patch- and skin prick testing (as there can be overlap clinically with contact urticaria). Other skin conditions may contribute to the skin problem, such as psoriasis or fungal infections and this can cause diagnostic uncertainty.

ACD is classically characterized by an erythematous, dry, scaly eruption, which is localized to the site of exposure (see Fig. 1). Although the site may suggest reactions to particular allergens (e.g. an eruption around the umbilicus may suggest an ACD to nickel from a belt buckle or clothes fasteners), the morphology of the eruption is unreliable in predicting whether the cause is allergic, irritant, endogenous or a combination [10]. Sometimes, localized exposure can ultimately result in a generalized eruption.

Confusingly, there are a number of distinct skin responses to type IV allergy other than the classical eczematous type. These include formation of blisters, pustules, hyperpigmentation or hypopigmentation, amongst others. The eruption may also become secondarily infected, usually with Staphylococcus aureus. Indications for patch testing include the following: dermatitis with an unusual distribution (or particularly localized); severe or treatment-resistant dermatitis; where they may be an occupational component or where either the clinician or the patient suspects allergy as contributing to the eruption.

Testing

Patch testing is a biological provocation test which has evolved into a standardized way of investigating type IV hypersensitivity reactions. Variables in the testing include the test system, test material, biological or functional status of the patient being tested and the person evaluating the results [11]. The gold standard test system (others do exist) occludes allergens (at known concentrations in an optimal vehicle) under aluminium discs (Finn chambers®, Epitest Oy, Tuusula, Finland) secured with an adhesive dressing (Scanpor® tape, Norgesplaster, Vennesla, Norway) for 2 days. At this time, the chambers are removed to see if early reactions are present and extra tests are applied if required. According to the criteria of the International Contact Dermatitis Research Group, a second reading should take place, typically at day 4 or 5, although later readings may also be indicated when testing with certain allergens. Testing takes place on the upper back (the best site for reproducibility and also, conveniently, being a large, flat surface), but other sites such as the arms, legs and abdomen may be used if necessary. The test area is marked, so that allergens may be identified at reaction sites. The tested area should be kept dry,

initially, to ensure adequate contact of the allergen with the skin, but ultimately to ensure that the identification markings are preserved. Other practical considerations include the following:

- Allergens must be sourced from a reputable company and usually require refrigeration.
- Testing should never take place on unknown substances.
- Published concentrations of most allergens are available [12]. This reference also gives the optimal vehicle(s) e.g. white petrolatum, water, alcohol, methyl ethyl ketone etc.
- It is often important to test to the patient's own products, however, they may need to be diluted appropriately.
- The back may need to be cleansed prior to application of allergens if oily and hairy backs may need to be clipped (not shaved) to ensure adequate occlusion.
- Patch testing should be deferred if the skin is heavily tanned (due to immunosuppression and potential false negative reactions).
- Ideally, patch testing should not take place when the patient has used potent corticosteroid creams on the test area in the days prior to testing. Antihistamines may be continued throughout testing.
- Oral corticosteroid use with Prednisolone >10 mg daily is a relative contraindication to testing, as it is known to suppress positive reactions [13]. Positive patch test results can be seen in patients on other immunosuppressives, if there is no possibility of stopping them [14].
- Patch testing is generally avoided in pregnancy, although there is no strong evidence of any deleterious effects.

Readings are performed generally on days 2 and 4 and are classified according to the strength of the reaction (see Table 1). The International Contact Dermatitis Research Group criteria are arbitrary and sometimes for research purposes, more detailed scales are employed. The search for a less subjective scoring system (e.g. using erythema sensors etc.) has not yet led to a practical solution. Interpretation of these reactions is sometimes difficult as irritant reactions can mimic true allergic responses closely. Knowing which chemicals are irritant can be helpful, as can the time course of reactions (e.g. crescendo response). Sometimes serial dilutions are required to be absolutely sure, especially with new allergens. False negatives may more readily occur if sites other than the upper back are used for testing (as is sometimes necessary due to florid dermatoses on the back).

The strength of the reaction on testing does not necessarily correlate with clinical relevance. Generally, weak responses are seen on patch testing with aminoglycoside allergy and these may, nevertheless, be a clinically relevant cause of eyelid eczema from an eye-drop or otitis externa from an ear-drop. With para-Phenylenediamine allergy from hair dyes, although, increasing strength of patch test allergic reactions means that the patient is increasingly unlikely to continue dyeing their hair, i.e. with weaker reactions, the patient may ignore mild symptoms of itch or discomfort and continue to dye their hair, whereas stronger reactions in real life cannot be ignored.

Table 1. Classification of patch test readings according to International Contact Dermatitis Research Group criteria: differentiating allergic from irritant reactions can be difficult

Reaction	Definition
?+	Doubtful reaction; faint erythema only
+	Weakly positive reaction; erythema, infiltration, possible papules
++	Strongly positive reaction; erythema, infiltration, papules, vesicles
+++	Extreme positive reaction; intense erythema and infiltration and coalescing vesicles
–	Negative reaction
IR	Irritant reaction
NT	Not tested

Sensitivity and specificity for the tests vary according to the individual items tested, however, some data from analysing common baseline series suggest a sensitivity of 0.77 and a specificity of 0.71 [15]. However, it is likely that this varies considerably from centre to centre depending on overall numbers tested, referral patterns etc.

Assessment of clinical relevance

The interpretation of results is critical. Not all positive reactions will be of current relevance. Some reactions may be clinically irrelevant cross-reactions. Sometimes a repeated open application test is required to establish relevance convincingly. This involves applying the suspect item to the volar aspect of the forearm in the same place twice a day for up to 2 weeks (or until an eczematous reaction occurs). If the patient has reacted to a fragrance chemical which is a listed ingredient of a deodorant, the product itself can be applied in the repeated open application test to establish relevance definitively. Sometimes, if the concentration of the fragrance chemical in the product is low (i.e. below the elicitation threshold), the patient may be able to tolerate it. The advice given to patients is also critical, as exhaustive lists are commonly forgotten by the patient, in the author's experience, and may be positively misleading. Giving simple written advice, tailored to the individual, is best.

The European baseline series

The European baseline series (see Table 2) is an array used for screening purposes in the investigation of suspected ACD. Some of the items are individual allergens and some are screening mixes, which have been designed to maximize sensitivity but to limit false positive (irritant) reactions. Patch test concentrations are always a compromise between keeping sensitivity high and irritant reactions infrequent. The chemicals in the series include fragrance ingredients, plant extracts, corticosteroids, preservatives, dyes, rubber accelerators, metals and others. The baseline series is the starting block for investigation and other series (both commercially available and otherwise) may need to be tested as well, including the patient's own items. In testing the patient's own products, care must be taken to ensure that the chemicals are not known irritants and that appropriate dilutions are made when necessary.

Table 2. The European baseline series

Name of allergen/mix	Patch test concentration and vehicle
Potassium dichromate	0.5% pet
Neomycin sulphate	20% pet
Thiuram mix	1% pet
p-Phenylenediamine free base	1% pet
Cobalt chloride	1% pet
Benzocaine	5% pet
Formaldehyde	1% aq
Colophonium	20% pet
Clioquinol	5% pet
Myroxylon pereirae	25% pet
N-isopropyl-*N*-phenyl-para-phenylenediamine	0.1% pet
Wool alcohols	30% pet
Mercapto mix	1% pet
Epoxy resin	1% pet
Paraben mix	16% pet
Para-Tertiary-butylphenol-formaldehyde resin	1% pet
Fragrance mix I	8% pet
Quaternium-15	1% pet
Nickel sulphate	5% pet
Methylchloroisothiazolinone and methylisothiazolinone	0.01% aq
Mercaptobenzothiazole	2% pet
Primin	0.01% pet
Sesquiterpene lactone mix	0.1% pet
Budesonide	0.1% pet
Tixocortol pivalate	1% pet
Methyldibromo glutaronitrile	0.3% pet
Hydroxyisohexyl-3-cyclohexene carboxaldehyde	5% pet
Fragrance mix II	14% pet

Pet, white petrolatum; aq, water.

Other series

Baseline series only screen for a limited number of allergens, and particular series have been designed to screen in more depth in particular situations, e.g. a patient with a persistent lichenoid eruption of the buccal mucosa adjacent to a dental prosthesis may be tested to a dental series of metals and dental cements, as well as a baseline series. Almirall Hermal and Chemotechnique have commercially available series (e.g. hairdresser, plastics, sunscreen ingredients, plants etc.), however, many large units have modified such series to account for allergens with local relevance. The patient's own products may also be tested, and this can be very helpful to establish relevance of the reaction.

Morbidity and mortality of testing

There are a number of adverse events potentially associated with patch testing, apart from false positive and negative results. Occluding the back itself can cause a flare of dermatitis, especially in atopics. Sometimes testing proves impossible for this reason. Occasionally reactions can be very strong with blistering, causing intense itch or pain and may become secondarily infected. Extremely rarely, this can cause permanent problems such as dyspigmentation and keloid formation. Although even strong reactions settle within a few days, some positive reactions can persist for over a year (e.g. gold). Very rarely, patients can become allergic to a particular substance from the patch test itself (a phenomenon known as active patch test sensitization). There have been isolated reports of type I reactions on testing including anaphylaxis (e.g. to drugs, antiseptics etc.) [16] so a thorough history must be taken before testing to decide whether or not patch tests are appropriate. The tests must take place in an environment where resuscitation can be undertaken if need be. Patch testing is a complex procedure that should be undertaken only by those adequately trained, as the person performing the tests is legally responsible for the consequences of testing.

Patch tests in children

ACD in the paediatric population is more common than previously recognized, and can manifest as a serious challenge for both patients and physicians. For children, the same preparations of allergens and test techniques can be used as for adults. Patch tests should be done with allergens suggested by history and with a shortened standard series (e.g. avoiding hair dye chemicals).

In children suspected to have ACD, 61% were confirmed to have a positive reaction to at least one

allergen. The utility of patch testing children whose clinical presentation is suggestive for ACD is high [17].

Sensitization to contact allergens may begin in infancy and becomes more common with advancing age. In recalcitrant atopic dermatitis, especially at the age of 5 years and over, patch tests are indicated. Contact allergy should be considered in all children with recalcitrant dermatitis. Good information on preventing the development of ACD in children is useful for carers [18].

Public health and legislative issues

Whilst patch testing is primarily about identifying existing allergies, information about trends in ACD can be helpful for primary prevention. The Health and Occupation Reporting Network (and its constituent national skin disease surveillance programme, known as EPIDERM) regularly publishes information to enable public health- and occupational physicians together with dermatologists to help prevent skin disease such as ACD at work. Supra-nationally, on the basis of epidemiological work on contact allergy, the European Union has enacted legislation to control exposure to many different allergens. Opinions are posted on the internet (e.g. see http://ec.europa.eu/health/ph_risk/committees/04_sccp/sccp_opinions_en.htm). The seventh amendment to the Cosmetics Directive enforced mandatory ingredient labelling of toiletries (e.g. preservatives or fragrance ingredients), allowing the consumer to avoid known allergens effectively. The Nickel Directive has reduced the amount of releasable nickel in items designed to be worn in close contact with the skin. Preliminary studies suggest that such legislation is successful in reducing the burden of contact dermatitis, even over a relatively short space of time [19]. It should be noted, though, that the frequency of contact allergy is typically higher in patch test populations than in the general population. There are few large studies looking at general populations [20].

Current resources for contact allergy

The European Society of Contact Dermatitis (ESCD) holds biennial meetings providing a forum for presentation of important work in this field. Initially a newsletter typed by enthusiasts and circulated by post, the target journal for research is Contact Dermatitis (a Wiley Blackwell publication, which is now the official publication of the ESCD). The most recent impact factor for the journal is 3.47, ranking 6/17 for allergy journals and 5/43 for dermatology journals. Another group (the European Environmental and Contact Dermatitis Research Group) promotes international collaborative studies.

Conclusions

Patch testing is a complex, but validated process for the investigation of type IV hypersensitivity. Testing should only be undertaken by those who have adequate training in this field and the risks and benefits of testing should be discussed with the patient beforehand. Routine testing where there is no real indication should be discouraged. Interpreting the results is an important part of the process and short, targeted written advice needs to be given to the patient at the end of the test period. Trends in ACD can lead to the implementation of effective legislation at national and supra-national level as primary prevention measures.

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